

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 17956A-5PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 18170	International filing date (day/month/year) 30/06/2000	(Earliest) Priority Date (day/month/year) 02/07/1999
Applicant BAYER AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

METHODS FOR MODULATING ANGIOGENESIS BY USING THE ANTI-ANGIOGENIC ANGIOTENSIN-7 AND POLYNUCLEOTIDES ENCODING THEREFOR

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☒ because this figure better characterizes the invention.

2
☐ None of the figures.

INTERNATIONAL SEARCH REPORT

Interr. Application No

PCT/US 00/18170

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/515 A61K38/00 A61P35/00 C12N15/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBL, GENSEQ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 15653 A (FERRARA NAPOLEONE ; GENENTECH INC (US); SCHWALL RALPH (US); BOTSTEI) 1 April 1999 (1999-04-01) cited in the application page 30, line 3 -page 31, line 16 page 35, line 6-19 examples 5-8,14,15	1-5, 8-20, 23-33
Y	claims 33-36 page 40, line 28 -page 41, line 23 page 34, line 18,19,37,38 --- -/--	1-33

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

4 December 2000

Date of mailing of the international search report

12/12/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

ALCONADA RODRIG., A

INTERNATIONAL SEARCH REPORT

Interr. Application No.

PCT/US 00/18170

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MAISONPIERRE P C ET AL: "ANGIOPOIETIN-2, A NATURAL ANTAGONIST FOR TIE2 THAT DISRUPTS IN VIVO ANGIOGENESIS" SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 277, 4 July 1997 (1997-07-04), pages 55-60, XP002046280 ISSN: 0036-8075 cited in the application page 58, left-hand column, paragraph 2 -page 59, left-hand column, paragraph 1; figure 7	1-5, 8-20, 23-33
Y	WO 99 26480 A (GENETIX PHARMACEUTICALS INC ;MASSACHUSETTS INST TECHNOLOGY (US)) 3 June 1999 (1999-06-03) page 14, line 15 -page 15, line 4 example 6 claims 1-17	6,7,21, 22
P,X	WO 00 21986 A (INCYTE PHARMA INC ;KLINGLER TOD M (US); VOLKMUTH WAYNE (US); WALKE) 20 April 2000 (2000-04-20) page 16, line 27 -page 17, line 1 page 28, line 6-20	32,33
T	WO 99 62925 A (HEUER JOSEF GEORG ;LEONARD REBECCA ANN (US); LILLY CO ELI (US); BU) 9 December 1999 (1999-12-09) claims 28,29 SEQ ID NOs: 1,2	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. Application No

PCT/US 00/18170

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9915653 A	01-04-1999	US 5972338 A US 6057435 A AU 9388098 A EP 1015585 A	26-10-1999 02-05-2000 12-04-1999 05-07-2000
WO 9926480 A	03-06-1999	AU 1598599 A	15-06-1999
WO 0021986 A	20-04-2000	AU 6417799 A EP 1037915 A	01-05-2000 27-09-2000
WO 9962925 A	09-12-1999	AU 4320499 A EP 0962530 A	20-12-1999 08-12-1999

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 23 May 2001 (23.05.01)	
International application No. PCT/US00/18170	Applicant's or agent's file reference 17956A-5PC
International filing date (day/month/year) 30 June 2000 (30.06.00)	Priority date (day/month/year) 02 July 1999 (02.07.99)
Applicant FRIEDRICH, Gabi et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:19 December 2000 (19.12.00)☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Antonia Muller Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

PCT

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLE

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office,
PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 20 August 2001 (20.08.01)	
Applicant's or agent's file reference 17956A-5PC	REPLY DUE see paragraph 1 below
International application No. PCT/US00/18170	International filing date (day/month/year) 30 June 2000 (30.06.00)
Applicant BAYER AG	

- ☐ REPLY DUE within _____ months/days from the above date of mailing
☐ NO REPLY DUE, however, see below
☒ IMPORTANT COMMUNICATION
☐ INFORMATION ONLY

2. COMMUNICATION:

Two demands for international preliminary examination have been filed in connection with the above-mentioned international application. The first demand was filed on 02 July 1999 with the IPEA/US and the second one was filed on 24 January 2001 with IPEA/EP. Both IPEA's are competent for carrying out the examination under the PCT for the international application.

The PCT does not specifically provide for the filing of two demands for the same international application. The meeting of International Authorities (Meeting of the Offices acting in the capacity of international Searching Authorities and International Preliminary Examining Authority under the PCT) considered the question in June 1993 and decided to proceed as indicated in the report of that meeting (see paragraphs 62-65).

Both International Preliminary Examination Reports will be transmitted to the elected offices under PCT. It is left to each elected Office to decide how to treat the two reports.

A copy of this communication is also being sent to the elected Offices and both IPEAs (IPEA/US and IPEA/EP).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Simin Baharlou
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

RECEIVED
OCT 30 2001BAYER CORPORATION
PATENT DEPARTMENT
BERKELEY, CALIFORNIAFrom the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITYTo:
MELISSA A. SHAW
BAYER CORPORATION
800 DWIGHT WAY
P.O. BOX 1986
BERKELEY, CA 94701

PCT

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

26 OCT 2001

Applicant's or agent's file reference

17956A-5PC

IMPORTANT NOTIFICATION

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US00/18170

30 June 2000 (30.06.2000)

02 July 1999 (02.07.1999)

Applicant

BAYER AG

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Form PCT/IPEA/416 (July 1992)

Authorized officer

Gary B. Nickol Ph.D.


Telephone No. 703-308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 17956A-SPC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/18170	International filing date (day/month/year) 30 June 2000 (30.06.2000)	Priority date (day/month/year) 02 July 1999 (02.07.1999)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 39/00, 39/02 and US Cl.: 424/185.1, 200.1		
Applicant BAYER AG		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>3</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of ___ sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>		
Date of submission of the demand 19 December 2000 (19.12.2000)	Date of completion of this report 20 September 2001 (20.09.2001)	
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Gary B. Nickol Ph.D.  Telephone No. 703-308-0196	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/18170

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.☒ the description:pages 1-59 as originally filedpages NONE filed with the demandpages NONE filed with the letter of _____☒ the claims:pages 60-62 as originally filedpages NONE as amended (together with any statement) under Article 19pages NONE filed with the demandpages NONE filed with the letter of _____☒ the drawings:pages 1-7 as originally filedpages NONE filed with the demandpages NONE filed with the letter of _____☒ the sequence listing part of the description:pages 1-13 as originally filedpages NONE filed with the demandpages NONE filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.☒ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4. ☐ The amendments have resulted in the cancellation of:☐ the description, pages NONE☐ the claims, Nos. NONE☐ the drawings, sheets/fig NONE5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

WRITTEN OPINION

International application No.
PCT/US00/18170

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims <u>6-7, 21-22</u>	YES
	Claims <u>1-5, 8-20, 23-33</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-33</u>	NO
Industrial Applicability (IA)	Claims <u>1-33</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-5, 8-20, and 23-33 lack novelty under PCT Article 33(2) as being anticipated by GODOWSKI et al. (WO 99/15653), 01 April 1999. Godowski et al. teach methods of inhibiting angiogenesis (including inhibiting tumor growth and endothelial cell proliferation) comprising administering to a mammal a therapeutically effective dose of an isolated Ang-7 polypeptide, a fragment, variant, derivative or analog thereof including the polypeptide of SEQ ID NO: 2. (see Figure 3). Godowski et al. further teach recombinant expression of the polypeptide in various host cells (pages 30-35 and examples 5-8, 14-15).

Claims 1-33 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of LEBOULCH et al. (WO.99/26480), 03 June 1999. Leboulch et al. teach gene therapy of anti-angiogenic molecules including recombinant expression in-vivo (pages 14 and 15) and ex-vivo applications (see Claims, pages 29-34).

Claims 1-33 meet industrial applicability as defined by PCT Article 33(4).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14
REC'D 30 OCT 2001

WIPO

PCT


Applicant's or agent's file reference 17956A-5PC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/18170	International filing date (day/month/year) 30 June 2000 (30.06.2000)	Priority date (day/month/year) 02 July 1999 (02.07.1999)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 39/00, 39/02 and US Cl.: 424/185.1, 200.1		
Applicant BAYER AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
 - ☒ Basis of the report
 - ☐ Priority
 - ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
 - ☐ Lack of unity of invention
 - ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - ☐ Certain documents cited
 - ☐ Certain defects in the international application
 - ☐ Certain observations on the international application

Date of submission of the demand 19 December 2000 (19.12.2000)	Date of completion of this report 20 September 2001 (20.09.2001)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Gary B. Nickol Ph.D.  Telephone No. 703-308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/18170

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed.
- ☒ the description:
 - pages 1-59 _____ as originally filed
 - pages NONE _____, filed with the demand
 - pages NONE _____, filed with the letter of _____
- ☒ the claims:
 - pages 60-62 _____, as originally filed
 - pages NONE _____, as amended (together with any statement) under Article 19
 - pages NONE _____, filed with the demand
 - pages NONE _____, filed with the letter of _____
- ☒ the drawings:
 - pages 1-7 _____, as originally filed
 - pages NONE _____, filed with the demand
 - pages NONE _____, filed with the letter of _____
- ☒ the sequence listing part of the description:
 - pages 1-13 _____, as originally filed
 - pages NONE _____, filed with the demand
 - pages NONE _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in printed form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).
 ** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

WRITTEN OPINIÓN

International application No.
PCT/US00/18170

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims <u>6-7, 21-22</u>	YES
	Claims <u>1-5, 8-20, 23-33</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-33</u>	NO
Industrial Applicability (IA)	Claims <u>1-33</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-5, 8-20, and 23-33 lack novelty under PCT Article 33(2) as being anticipated by GODOWSKI et al. (WO 99/15653), 01 April 1999. Godowski et al. teach methods of inhibiting angiogenesis (including inhibiting tumor growth and endothelial cell proliferation) comprising administering to a mammal a therapeutically effective dose of an isolated Ang-7 polypeptide, a fragment, variant, derivative or analog thereof including the polypeptide of SEQ ID NO: 2. (see Figure 3). Godowski et al. further teach recombinant expression of the polypeptide in various host cells (pages 30-35 and examples 5-8, 14-15).

Claims 1-33 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of LEBOULCH et al. (WO 99/26480), 03 June 1999. Leboulch et al. teach gene therapy of anti-angiogenic molecules including recombinant expression in-vivo (pages 14 and 15) and ex-vivo applications (see Claims, pages 29-34).

Claims 1-33 meet industrial applicability as defined by PCT Article 33(4).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 18 OCT 2001

WIPO PCT

Applicant's or agent's file reference Le A 33 752-WO Bu		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/18170	International filing date (day/month/year) 30/06/2000	Priority date (day/month/year) 02/07/1999
International Patent Classification (IPC) or national classification and IPC C07K14/515		
Applicant BAYER AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 24/01/2001	Date of completion of this report 16.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fayos, C Telephone No. +49 89 2399 2180



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/18170

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
- Description, pages:**

1-59 as originally filed

Claims, No.:

1-33 as originally filed

Drawings, sheets:

1/7-7/7 as originally filed

Sequence listing part of the description, pages:

1-13, filed with the letter of 15.09.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/18170

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
- ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application.
- ☒ claims Nos. 1-33 (industrial applicability).

because:

- ☒ the said international application, or the said claims Nos. 1-33 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/18170

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6-7 and 21-22
	No:	Claims	1-5, 8-20 and 23-33
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	-

2. Citations and explanations **see separate sheet**

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/18170

Re Item II

Priority

1- Priority

- 1- Only the subject matter indicated in item 1.2- below, is entitled the claimed priority date of 02.07.1999 because it is disclosed in the priority document.
- 1.1- For the subject matter for which the priority claimed is invalid, the effective date of the application is the filing date 30.06.2000. Therefore, D4 which was published on the 20.04.2000 constitutes prior art pursuant to Rule 64.1 PCT for said subject matter.
- 1.2- The referred subject matter (item 1- above) for which priority is valid is the following: a nucleic acid molecule encoding human Ang-7, methods for producing recombinant human Ang-7 protein (examples 1-3), therapeutic compositions as well as a method for modulating angiogenesis (not detailed in the priority document).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- 2- Claims 1-33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 3- Reference is made to the following documents:

- D1: WO 99 15653 A (FERRARA NAPOLEONE ;GENENTECH INC (US); SCHWALL RALPH (US); BOTSTEI) 1 April 1999 (1999-04-01) cited in the application
- D2: WO 99 26480 A (GENETIX PHARMACEUTICALS INC ;MASSACHUSETTS INST

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/18170

TECHNOLOGY (US)) 3 June 1999 (1999-06-03)

D3: WO 99 62925 A (HEUER JOSEF GEORG ;LEONARD REBECCA ANN (US); LILLY CO ELI (US); BU) 9 December 1999 (1999-12-09)

D4: WO 00 21986 A (INCYTE PHARMA INC ;KLINGLER TOD M (US); VOLKMUTH WAYNE (US); WALKE) 20 April 2000 (2000-04-20)

D5: MAISONPIERRE P C ET AL: 'ANGIOPOIETIN-2, A NATURAL ANTAGONIST FOR TIE2 THAT DISRUPTS IN VIVO ANGIOGENESIS' SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 277, 4 July 1997 (1997-07-04), pages 55-60, XP002046280 ISSN: 0036-8075 cited in the application

NOVELTY - Art. 33 (1) and (2) PCT

4- Claims 1-5, 8-20, 23-33 lack novelty for the reasons stated below

4.1- D1 provides the sequence of NL-1 TIE ligand which is identical to Ang-7 and claims its use to inhibit angiogenesis (p 30 line 3 - p 31 line 16, p 35 line 16-19 and claims. However, experimental data with NL-1 show either a stimulatory effect on tumor growth (example 14) or inconclusive data on endothelial tube formation (example 15.3).

Hence, D1 anticipates the subject matter of claims 1-5, 8-20 and 23-33 which therefore lack novelty.

4.2- D4 provides the sequence of the polynucleotide NSEQ-11 coding for the polypeptide NPEP-23 with shows 100% identity with SEQ ID NO:2 of the present application (Ang-7) over its entire lenght. D4 identifies homology of NPEP-11 with angiopoietin and claims uses thereof to treat cancer.

Therefore, in view of item II 1.2- above, claims 32-33 lack novelty in the light of D4.

4.3- Claims 6-7 and 21-22 appear to be novel over the prior art cited in the search report. The novel features are: a method for inhibiting angiogenesis comprising administering ex vivo to a mammal a therapeutically effective dose of an isolated Ang-7 polypeptide, a fragment, variant derivative or analog thereof.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/18170

INVENTIVE STEP - Art. 33 (1) and (3) PCT

5- Claims 1-33 lack inventive step for the reasons stated below:

- 5.1- The closest prior art is represented by D2, which provides the sequence of angiopoietin-2 and reports its function as a TIE-2 antagonist and angiogenesis inhibitor in vivo.

The closest prior art differs from the present application in that it does not disclose Ang-7.

The technical effect achieved in the present application is not different from that of D2.

The present application is based on the identification of Ang-7 as member of the angiopoietin ligand family, based on its similarity to Ang-1.

The objective problem posed in the present application is to provide further members of the angiopoietin ligand family (TIE-2 antagonists; angiogenesis inhibitors in vivo).

The solution proposed is Ang-7.

- 5.2- In the light of the teachings of D2, the skilled man, having the sequence NL-1 shown in D1 and the suggestion that these polypeptides work as angiogenesis inhibitor, would use the methods reported in D2 to assess the potential anti-angiogenic activity of NL-1.

Furthermore, D3 discloses a method of anti cancerogenic gene therapy using ex vivo administration of cell transformed with a vector encoding an anti-angiogenic polypeptide. Thus, the skilled person would also apply this method in order to inhibit angiogenesis using the angiogenesis inhibitor of D1, as mentioned above.

- 5.3- Claims 1-33 lack therefore inventive step.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/18170

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

- 6- For the assessment of the present claims 1-33 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

- 7- Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO0021986	20.04.2000	06.10.1999	09.10.1998